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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,681	09/26/2005	Jerachmiel (Yori) Appelbaum	090-ATH	8344

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EXAMINER	
PACKARD, BENJAMIN J	

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1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,681	APPELBAUM, JERACHMIEL (YORI)	
	Examiner	Art Unit	
	Benjamin Packard	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-56* is/are pending in the application.

4a) Of the above claim(s) *34-43,55 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 02/05/09, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

New Claims 34-43 and 55-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) where claims 34-43 are drawn to a nonelected invention and claims 55-56 are drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/29/08.

Claim Rejections - 35 USC § 112 – Written Description

Claim 44 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals

appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as TPEN "derivative" used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus.* See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the

method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

Here, the specification does not provide a reasonably representative disclosure of useful TPEN derivatives generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species at page 16, last paragraph, and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

Claim Rejections - 35 USC § 112 – New Matter

Claims 48-50 and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 48 is directed to "selectively prevent capillary formation", but the specification does not appear to support such a limitation.

Claim 49 is directed to the inhibiting the spread of cancer by preventing capillary formation by the prevention of capillary formation, which does not appear to be supported by the specification.

Claim 52 is directed to a higher affinity which enables normal physiological function. While paragraph 50 of the Pregrant pub teaches calcium chelation issues can be overcome when using TPEN, that does not support the broader "normal physiological function" language instantly claimed.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the risk of tumor cellular invasion and tumor mestastasis, does not reasonably provide enablement for prevention of the same or prevention of the diseases/disorders of claim 53. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The invention relates to the prevention of tumor cellular invasion and/or tumor metastasis, as well as the treatment and/or prevention of the disease/disorders of claim 53. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Suggitt and Bibby, *Clinical Cancer Research*, Vol 11, 971-981. Suggitt and Bibby teaches the unpredictability of treating cancer, which includes cancer at the metastasis phase. Note however, that the current human tumor cell line in vitro screen is generally unpredictable. Modern methods are susceptible to false-positive and false-negative results. (page 973 1st paragraph on right-hand column). Difficulty in determining results leads to difficulty in testing for effectiveness of compounds, which leads to unpredictability in treating cancers.

2. The breadth of the claims

The claims are broad insofar as they are directed to the prevention of tumor cellular invasion and/or tumor metastasis, as well as the treatment/prevention of the diseases and/or disorders of claim 53.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for preventing tumor cellular invasion and/or tumor metastasis, or the treatment/prevention of the diseases and/or disorders of claim 53. There are not working examples, only teaching how to test on animal models.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent tumor cellular invasion and/or tumor metastasis of the secondary treatment/prevention of the diseases and/or disorders of claim 53. as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 44-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al (Biochemical and Biophysical Research Communications, Vol 297, Iss 4, (2002) 1062-1070) in view of Krajewska et al (Cancer Research 57:8 (1997) 1605-1613).

Carter teaches depletion of intracellular Zn2+ in sheep AEC, using the membrane permeant Zn2+ chelator TPEN, increased lipid peroxidation in the apical cell membranes (as assessed by immunofluorescence with anti-hydroxynonenal) as well as increasing activated pro-caspase-3 and apoptosis (abstract). Carter et al relates the sheep model to NCI-H292 cells for reducing Zn2+ concentrations (pg 1066, Induction of caspase-3 activation in AEC by Zn depletion section). NCI-H292 cells are stated to be derived from cervical node metastasis of a pulmonary mucoepidermoid carcinoma

(page 1063, right column, Cell lines). Zn2+ is additionally taught as a known suppressor of apoptosis (page 1069 about lines 21-30).

Carter et al does not teach the treatment of a mammal.

Krajewska et al teaches the correlation between patterns of caspase-3 concentration and cell death in a variety of cell lines, including cells of the pulmonary system where caspase-3 is present in the immunostaining (see pg 1610 discussion, second full paragraph and pg 1607 Pulmonary System).

One of ordinary skill would have a reasonable expectation of success where the pulmonary cells are taught to have caspase-3 present and the mechanism (i.e. caspase-3 activity) causes cell death in vivo.

Krajewska et al does not teach activating caspase-3 by Zn2+ depletion.

It would be obvious to one of ordinary skill in the art to use TPEN in treating metastasis of a pulmonary mucoepidermoid carcinoma, given the compound is able to reduce a suppressor of regular apoptosis which then reasonably increases regular cellular apoptosis, as evidenced by the secondary reference which provides a reasonably expectation of success for the treatment, given the same mechanism has in vivo-in vitro correlation.

Note, the mechanism of claim 48, and dependant claims 49 would be obvious to one of ordinary skill in the art where a composition with the same active agent claimed (TPEN) is administered to the same patient populations (mammals with metastasis species cancers), given the purpose of the method made obvious above is to prevent metastasis, i.e. the spreading of cancer, and claim 48 is simply directed to recognizing a

new mechanism (prevention of capillary formation) by which the method is accomplished. Recognition of a new pathway does not overcome the prima facia case of obviousness, where the motivation to practice the method for other reasons exists, i.e. to prevent metastasis.

Additionally, the properties of TPEN in claims 50-52 and 54 appear to be obvious given they are properties not of the composition, but of the single component (i.e. TPEN). As such, a compound and its properties cannot be separated.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-R 8-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
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